



Deposited via The University of Sheffield.

White Rose Research Online URL for this paper:

<https://eprints.whiterose.ac.uk/id/eprint/188124/>

Version: Accepted Version

Article:

Colton, H., Greenfield, D.M., Snowden, J.A. et al. (2021) Long-term survivors following autologous haematopoietic stem cell transplantation have significant defects in their humoral immunity against vaccine preventable diseases, years on from transplant. *Vaccine*, 39 (34). pp. 4778-4783. ISSN: 0264-410X

<https://doi.org/10.1016/j.vaccine.2021.07.022>

Article available under the terms of the CC-BY-NC-ND licence
(<https://creativecommons.org/licenses/by-nc-nd/4.0/>).

Reuse

This article is distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs (CC BY-NC-ND) licence. This licence only allows you to download this work and share it with others as long as you credit the authors, but you can't change the article in any way or use it commercially. More information and the full terms of the licence here: <https://creativecommons.org/licenses/>

Takedown

If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.

Long-term survivors following autologous haematopoietic stem cell transplantation have significant defects in their humoral immunity against vaccine preventable diseases, years on from transplant

Hayley Colton^{1,2}, Diana M. Greenfield³, John A. Snowden⁴, Paul D.E. Miller⁵, Nicholas J. Morley⁴, Josh Wright⁴, Thomas C. Darton^{1,2}, Cariad M. Evans⁶ & Thushan I. de Silva^{1,2}

1. Department of Infection, Immunity and Cardiovascular Diseases and the Florey Institute for Host-Pathogen Interactions, University of Sheffield, UK
2. South Yorkshire Regional Department of Infection & Tropical Medicine, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK
3. Specialised Cancer Services, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK
4. Department of Haematology, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK
5. Department of Haematology, St George's University Hospitals NHS Foundation Trust, London, UK
6. Department of Virology, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK.

Abstract 149/150

Current international guidelines recommend routinely vaccinating haematopoietic stem cell transplant (HSCT) recipients. Despite significant infection-related mortality following autologous HSCT, routine vaccination programmes (RVP) completion is poor. For recovered HSCT recipients seen years later, it is uncertain whether catch-up vaccination remains worthwhile.

To determine potential susceptibility to vaccine preventable infections, we measured antibody titres in 56 patients, a median of 7 years (range 0 – 29) following autologous HSCT, who had not completed RVP. We found that the vast majority had inadequate titres against diphtheria (98.2%) and *S.pneumoniae* (100%), and a significant proportion had inadequate titres against measles (34.5%). Of those subsequently vaccinated according to available guidelines, many mounted protective serological responses.

These data suggest a pragmatic catch-up approach for autologous HSCT recipients who have not completed RVP is advisable, with universal vaccination against some pathogens (e.g. *S.pneumoniae* and *diphtheria*) and serologically-guided approaches for others (e.g. measles and varicella zoster virus).

Body Word count 1994/2000, 4 tables/ figures, 20/20 references

Introduction

Despite advances in haematopoietic stem cell transplantation (HSCT), infection remains a substantial cause of late mortality in both allogeneic HSCT and autologous HSCT recipients[1,2]. As impaired humoral immunity can persist for years post-transplant, several best-practice international guidelines recommend routine vaccination programmes (RVP) in the months following HSCT to reduce the risk of vaccine preventable diseases (VPD)[1,3].

Although humoral antibody responses to VPD may reconstitute more readily following autologous HSCT compared to allogeneic HSCT, autologous recipients commonly lose their immunity, particularly if multiple chemotherapy regimens were given pre-transplantation[1]. Previous surveys of centres in the UK have shown that only ~50% recommended RVP following autologous HSCT, and RVP completion rates are often poor despite clinician awareness of their importance[4,5].

With increasing life expectancy post-HSCT, 'late-effects' clinics are increasingly important for managing transplant-related late sequelae. We were faced with a cohort of autologous HSCT recipients, some even decades post-transplant, who for various reasons missed RVP. Given there are no clear guidelines on how to approach these patients, we explored whether humoral immune responses against common VPD reconstitutes naturally in the absence of specific vaccination. In seronegative patients, we aimed to see whether a complete catch-up RVP or a more pragmatic targeted vaccination programme would be more appropriate.

Methods

Study participants and procedures: Following institutional approval, a 1-year observational study (15th May 2017 to 23rd May 2018) was conducted at Sheffield Teaching Hospitals NHS Foundation Trust of consecutive autologous HSCT patients attending a late-effects clinic as part of routine NHS care. These patients had not undergone a previous RVP post-transplant.

During clinic attendance, patients were asked about childhood vaccinations and blood was drawn to measure antibody titres against diphtheria, MMR (measles, mumps, rubella), varicella zoster virus (VZV), *Streptococcus pneumoniae* (12 Danish serotypes: 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23), tetanus and *Haemophilus influenzae* type B (Hib). Other VPD were not included in our study as testing is either based on the presence of specific risk factors (e.g. birthplace for hepatitis B), or antibody testing is not routinely available (e.g. polio, pertussis).

Antibody titre measurement and thresholds: Serology was performed using standard practice for our NHS laboratory (Supplementary Table 1). Definitions of protective thresholds were based on accepted levels in the literature, or on assay specific values (Table 1b). Thresholds for anti-tetanus IgG, anti-Hib IgG and anti-rubella IgG (≥ 0.1 IU/ml, ≥ 0.15 $\mu\text{g/ml}$ and ≥ 10 IU/ml, respectively) were based on previously defined cut-offs[6]. Although a protective anti-diphtheria IgG is frequently cited as ≥ 0.1 IU/ml, we used the WHO's threshold of ≥ 1.0 IU/ml, which is associated with long term protection[6,7]. Anti-measles and anti-mumps IgG were assay-specific cut offs (15 AU/ml and 10 AU/ml, respectively), and reported qualitatively. Defining protective correlates to *S. pneumoniae* was more challenging, as protective levels vary by serotype, patient age and comorbidities[6,8]. The WHO recommends a threshold of ≥ 0.35 $\mu\text{g/mL}$, however this is based on studies on infants[8]. The threshold for adults is unknown, as they have a higher level of circulating IgG yet have a greater incidence of pneumococcal disease, and even less is known about immunocompromised individuals[8]. A putative threshold of ≥ 1.0 $\mu\text{g/ml}$ has been suggested by multiple experts and was used in this study[9]. The protective VZV IgG threshold varies by age, ethnicity and whether immunity was acquired following infection or vaccination, however we opted to use our assays threshold of 150 mIU/ml which was based on previous studies[10,11].

Vaccinations: Recommendation for vaccination and post-vaccination serological testing were sent to the patient's general practitioner (GP) in accordance with published guidelines (Supplementary Table 1)[1,3,8,12]. Where vaccination was not available in primary care settings, patients were referred and vaccinated through the outpatient clinics in the infectious diseases department.

Follow up: One year following clinic attendance (15th May 2018 to 23rd May 2019), post-vaccination serology was reviewed and compared to pre-vaccination titres.

Analysis: Non-normally distributed continuous data were log transformed prior to analysis with parametric tests. Normally distributed continuous data were analysed using either a t-test (two group comparison), analysis of variance (three group comparison) or Pearson correlation. Categorical variables were analysed using chi-squared test. Univariate linear and logistic regression models were constructed to assess if any characteristics were associated with antibody titres (or seropositivity where results were qualitatively reported) for each VPD. Associations with p values ≤ 0.2 were assessed with multivariate analysis for each VPD. Statistical analysis was performed using R Studio version 1.1.463.

Results

Demographic and clinical details (Table 1): 60 sequential attendees were identified as suitable. As one patient had completed RVP elsewhere and three patients' blood samples were not received by the laboratory, 56 patients were included in the final analysis. Since live vaccines are contraindicated within two years of HSCT, one patient was excluded from the analysis for MMR and VZV[3]. One patient was excluded from the analysis for tetanus and Hib as incomplete testing occurred at clinic attendance.

The median patient age was 48 years (range 22 – 72), and most had received HSCT due to haematological malignancy (n=42, 75%). The median time from HSCT was 7 years, but some were decades post-transplant (range 0 – 29 years). Most patients had received pre-HSCT chemotherapy (n=52, 92.9%), and the majority reported completing their childhood vaccination schedule (n=34, 60.7%).

Proportion with adequate antibody titres (Table 2): The proportion of patients with antibody titres below defined protective thresholds varied across the VPDs tested.

Almost all patients did not achieve the 1.0 IU/ml threshold for diphtheria (n=55, 98.2%, 95% CI 90.4- 100.0%) and every patient had titres below 1.0 µg/mL for all 12 Danish pneumococcal serotypes (n= 56, 100%, 95% CI 93.6-100%). Only two patients (3.57%) even achieved the lower threshold of ≥ 0.35 µg/mL for all 12 pneumococcal serotypes (Fig 1a, Supplementary Table 2a).

In contrast, titres below the thresholds for Hib, VZV and tetanus were seen in fewer individuals (5.5%, 10.9% and 20% respectively). The MMR results were varied, with 34.5% of patients considered seronegative to measles, 50.9% to mumps and 29.1% to rubella.

Factors associated with antibody status (Supplementary Tables 3a and 3b): Significant associations on univariate analysis were found between measles seropositivity and increasing age (current age OR 1.09, p=0.005, 95% CI 1.03-1.15; age at transplant OR 1.07, p=0.008, 95% CI 1.02-1.13), and those who received BEAM conditioning were less likely to be mumps seropositive (OR 0.21, p=0.028, 95% CI 0.05-0.80). On multivariate analysis, these associations remained significant, and in addition those who received BEAM or TBI were more likely to be measles seronegative.

Follow up serology (Supplementary Table 4 and 5): In most cases, GPs were willing to facilitate administration of recommended vaccinations and follow up serology. Serology for at least one VPD was performed in 42 patients (75%), either by their GP or at subsequent clinic attendances. Increases were seen in post-vaccination titres against diphtheria and *S.pneumoniae* (Figs 1 and 2, Supplementary Fig 2). Univariate analysis revealed male patients were more likely to have an antibody response to diphtheria vaccination (OR 9.8, p=0.017, 95% CI 1.72-83.05), although this did not remain significant on multivariate analysis.

Discussion

Our cohort of autologous HSCT patients with a range of underlying diagnoses, who for various reasons missed post-transplant RVP, had significant defects in their humoral immunity against a number of common VPD (median 7, range 0 – 29 years post-transplant).

A prominent finding was an almost universal absence of adequate antibody titres against vaccine-serotype strains of *S. pneumoniae*, with only 3.57% achieving pre-vaccination titres greater than the WHO's paediatric threshold to all 12 Danish serotypes. This is concerning as invasive pneumococcal disease incidence is substantially higher in autologous HSCT recipients compared to the general population, and is a significant cause of morbidity and mortality[8,12]. Although serotype-specific antibody levels increased post-vaccination, only 20% achieved the WHO's paediatric threshold for all 12 serotypes. It is worth noting that while we advised the UK standard recommendation of 2 doses of pneumococcal vaccine, other guidance suggest more may be required to elicit a protective immune response[3,12].

Low levels of anti-diphtheria IgG was another common finding, and it was reassuring that our cohort responded well serologically post-vaccination. In other studies men were found to have higher circulating levels of anti-diphtheria IgG which fits with our post-vaccination findings[13].

Our measles results were varied, however a link was seen between increasing age and measles seropositivity. This supports other studies which found that individuals with previous measles exposure, who are usually older in age, were more likely to be measles seropositive post-HSCT when compared to their vaccinated counterparts[14]. MMR vaccination is not currently recommended for individuals who are seronegative to mumps or rubella if they are measles seropositive, so a significant proportion of our cohort could remain potentially susceptible to mumps and/or rubella(Supplementary Fig 1)[1,3]. The rationale may be that the correlates of protection for mumps and rubella are not as reliably defined as measles, plus the epidemiology and severity of each infection differs[6]. While there have been multiple outbreaks of measles and mumps in the UK, mumps case fatality is low in the HSCT population, whereas measles has a significantly higher morbidity and mortality[6,8,14]. The signal between conditioning regimens, and measles and mumps seronegativity could be explained by more intensive treatment and/or underlying transplant indications; however numbers within our study were small and this requires further investigation in a larger cohort.

On the whole, antibody titres within our post-HSCT cohort were lower than the published data available for the UK population and other immunosuppressed individuals who did not receive HSCT, however direct comparison is challenging due to the different thresholds used (Table 2)[13,15–19]. Interestingly, rates of diphtheria seronegativity were similar in our cohort to a study in Austria of patients with haematological malignancy who did not undergo HSCT, who used the same threshold and testing kit to our cohort[19].

The suboptimal antibody titres, particularly against diphtheria and *S. pneumoniae*, in our cohort who missed RVP favours efforts to optimise immunity in the months post-transplant through RVP. For HSCT recipients who missed RVP, other transplant centres may find 'late-effects' clinics as a good platform to screen and recommend pragmatic vaccination advice.

We suggest different approaches for different VPD for those who have not undergone RVP post-transplant. Universal pneumococcal and diphtheria vaccination without checking antibody titres may be a practical approach given the scarcity of adequate titres in our cohort. This recommendation would have the benefit of covering for other VPD within the diphtheria combination vaccine, which has particular relevance to our aging population of patients who likely have waning immunity to tetanus and pertussis, plus pertussis has had a recent upsurge in some developed countries[13,20]. Given most of our cohort had adequate antibody titres to measles and VZV, performing antibody testing prior to vaccination seems sensible given the incidence, morbidity and mortality of both infections[15,17]. As Hib titres were almost always adequate, our data suggests there may be little benefit to check titres or vaccinate, although equally there is probably no harm, and indeed Hib may be recommended in disease specific guidelines.

More evidence is needed to vaccinate based on immunity to mumps and rubella, and to determine the optimal pneumococcal vaccination dosing and timing. There is scope for future studies to compare antibody titres in those who did receive RVP versus those who did not, the immunogenicity of a pre- vs post-HSCT RVP, and to review post-vaccination antibody responses in the autologous HSCT population on a larger scale.

Conclusion

Recovered autologous HSCT recipients who had not received RVP post-transplant had significant defects in their humoral immunity against a number of common VPD despite being years post-transplant. Catch-up vaccination resulted in an increase in antibody titres. Whilst further evidence is required to guide vaccination in this setting, our study contributes to existing evidence that earlier strategies to optimise immunity in autologous HSCT patients are warranted.

For those who missed RVP, we suggest different approaches for each VPD, using late-effects clinics as a platform to screen and recommend vaccination. A pragmatic strategy could be to universally vaccinate against diphtheria and pneumococcal infection, and to target measles and VZV vaccination based on serostatus.

Tables and figures

Table 1. Clinical and demographics characteristics of HSCT patients

Age	Median in years (range)
At clinic attendance	48 (22 - 72)
At HSCT	37.5 (14 - 69)
Time from diagnosis to HSCT	1 (0 - 6)
Time since HSCT	7 (0 - 29)
Sex	n (%)
Male	26 (46.4)
Female	30 (53.6)
Childhood vaccination status	n (%)
Fully vaccinated	34 (60.7)
Not fully vaccinated	2 (3.6)
Patient unsure	20 (35.7)
Diagnoses	n (%)
Haemato-oncological Malignancies [‡]	42 (75.0)
Lymphoma	36
Myeloma	3
Acute Leukaemia	3
Solid Tumours [†]	10 (17.9)
Autoimmune Diseases ^ψ	4 (7.1)
Treatments received pre-HSCT	n (%)
Chemotherapy [#]	52 (92.9)
Radiotherapy [∅]	21 (37.5)
Rituximab	11 (19.6)
Conditioning regimens ^{&}	n (%)
BEAM	35 (62.5)
Other chemotherapy-only conditioning	13 (23.2)
TBI-containing conditioning	4 (7.1)
ATG-containing conditioning	4 (7.1)

Abbreviations: HSCT- Haematopoietic Stem Cell Transplant, TBI - total body irradiation, ATG -anti-thymocyte globulin

- [‡] Lymphomas: Hodgkin n= 18, Diffuse Large B-Cell n=8, Follicular n=6, Non-Hodgkin n=1, T-Cell Central Nervous System n=1, Enteropathy-Associated T-Cell n=1, Anaplastic Large Cell n=1.
Acute Leukaemias: Acute Myeloid Leukaemia n=2, Acute T-Cell Lymphoblastic Leukaemia n=1
- [†] Solid tumours: Gestational Trophoblastic Disease n=5, Testicular Teratoma / Germ Cell n=3, Neuroendocrine n=2
- ^ψ Autoimmune diseases: Multiple Sclerosis n=4
- [#] Regimens included **ESHAP** (etoposide, methylprednisolone, cytarabine, cisplatin; n=17), **cyclophosphamide** (n=9), **CHOP** (cyclophosphamide, doxorubicin, vincristine, prednisolone; n=8), **ABVD** (doxorubicin, bleomycin, vinblastine, dacarbazine; n=7), **methotrexate** (n=7), **R-CHOP** (rituximab plus CHOP; n=6), **Ch1VPPI** (chlorambucil, procarbazine, prednisolone, vinblastine; n=6), **EP/EMA** (etoposide/cisplatin, etoposide/methotrexate/dactinomycin; n=5), **PAB1OEI** (prednisolone, doxorubicin, bleomycin, vincristine, etoposide; n=5), **rituximab** (n=5), **TP/TE** (paclitaxel/cisplatin, paclitaxel/etoposide; n=4), **VAPEC-B** (vincristine, doxorubicin, prednisolone, etoposide, cyclophosphamide, bleomycin; n=3), **R-ESHAP** (rituximab plus ESHAP; n=2), **IVE** (ifosfamide, epirubicin, etoposide; n=2), **DHAP** (dexamethasone, cytarabine, cisplatin; n=2), **BEP** (bleomycin, etoposide, cisplatin; n=2) and **R-CVP** (rituximab, cyclophosphamide, vincristine, prednisolone; n=2).
- [∅] Radiotherapy - Mediastinal only n=5, Mantle n=4, Pelvis n=3, Neck only n=3, Mediastinum/Neck n=2, Whole Brain n=2, Para-aortic Nodes n=1, Stereotactic Radiosurgery of Brain n=1
- [&] BEAM conditioning regimen includes BiCNU® (Carmustine), Etoposide, Ara-C (Cytarabine) and Melphalan. Other conditioning chemotherapy agents were used either alone or in combination - melphalan, cyclophosphamide, carboplatin, etoposide, paclitaxel, ifosfamide and busulfan.

Table 2: Seronegativity in our study cohort compared to other cohorts in the literature

	STUDY GROUP		UK GENERAL POPULATION [13,15–18]		AUSTRIAN IMMUNOSUPPRESSED INDIVIDUALS (NO HSCT)[19]		
	%	Threshold	%	Threshold	SOLID MALIGNANCIES	HAEMATOLOGICAL MALIGNANCIES	Threshold
Diphtheria	98.2	1.0 IU/ml	N/A	-	N/A	N/A	-
	76.8	0.1 IU/ml	59	0.1 IU/ml	40.51	76.09	0.1 IU/ml
< 35 years	37.5	0.1 IU/ml	30	0.1 IU/ml	N/A	N/A	-
> 35 years	82.6	0.1 IU/ml	69 - 76	0.1 IU/ml	N/A	N/A	-
Tetanus	20.0	0.1 IU/ml	17	0.1 IU/ml	11.11	13.04	0.1 IU/ml
Measles	34.5	15 AU/ml	1 - 10	N/A	3.70 *	13.04*	275 IU/ml*
Mumps	50.9	10 AU/ml	N/A	-	12.73*	39.13*	22 RU/ml*
Rubella	29.1	10 IU/ml	N/A	-	17.17*	30.43*	26 IU/ml*
VZV	10.9	150 mIU/ml	1.6 - 10	N/A	11.83*	32.61*	400 IU/ml*
Pneumococcal	96.4	0.35 µg/ml	N/A	-	N/A	N/A	-
	100	1.0 µg/ml					
Hib	5.5	0.15 µg/ml	5		N/A	N/A	

N/A – Not available

* Different thresholds were used to define serostatus in our study so are difficult to directly compare

Fig 1: Percentage of patients with antibody titres against each Pneumococcal serotype, Pre- and Post- Vaccination

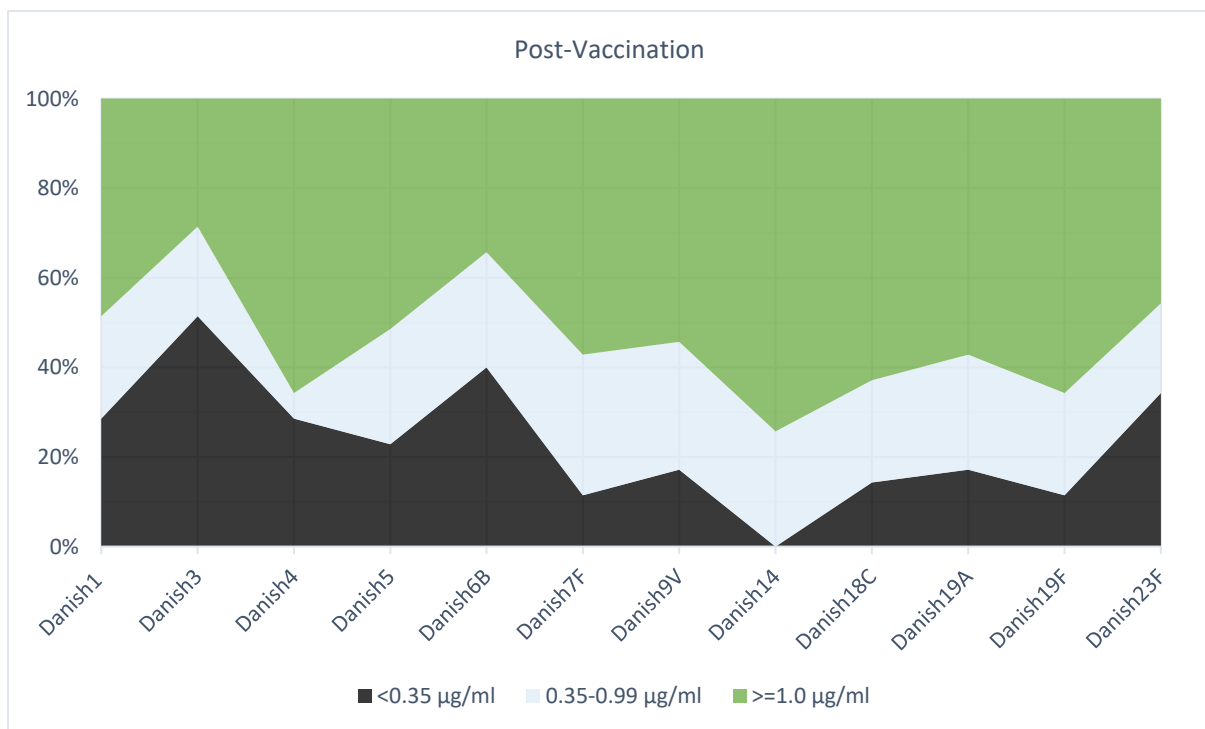
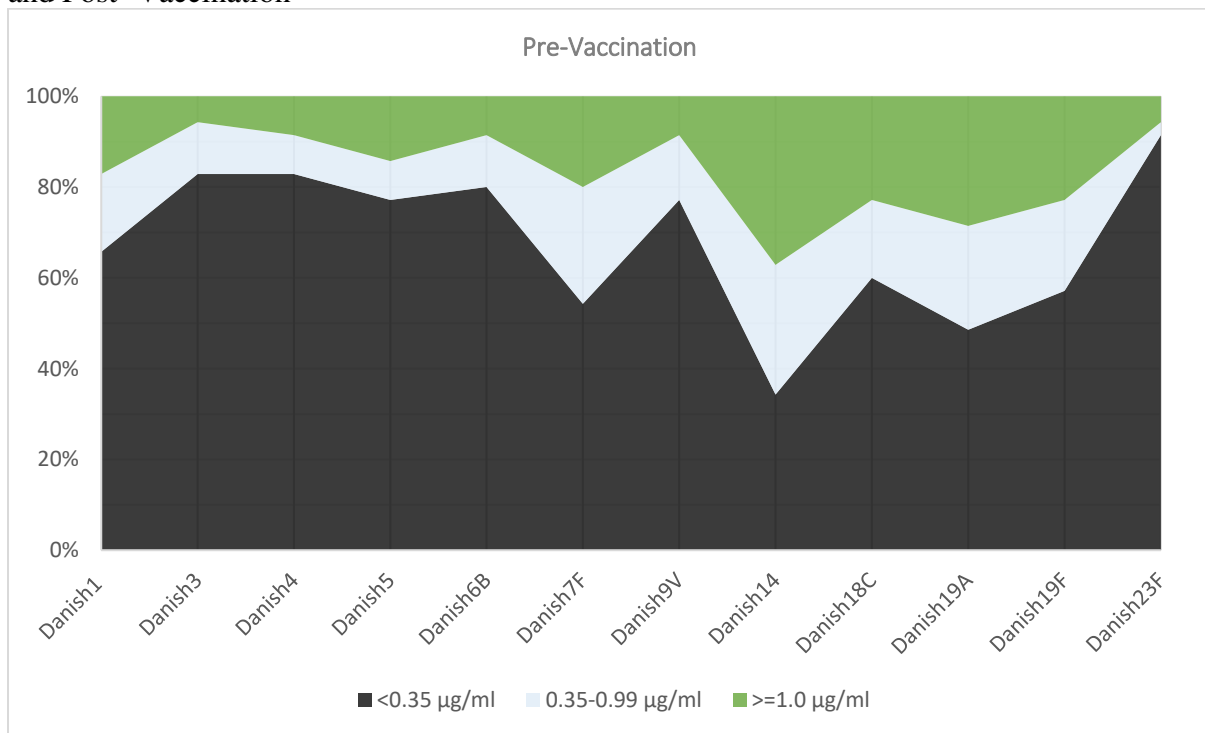
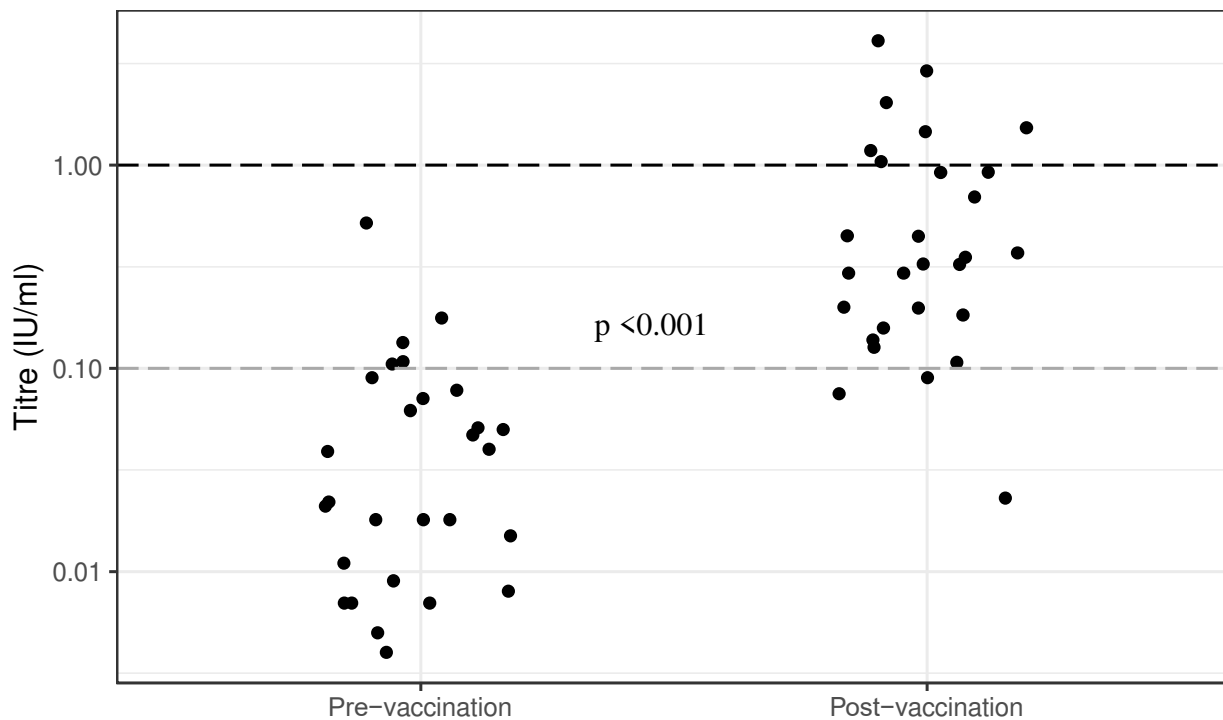


Fig 2: Comparison of Diphtheria antibody titres pre and post-vaccination



Supplementary Table 1: Summary of testing and vaccine recommendations

VPD	Serological Test	Coated Antigen	Threshold	Schedule	Guideline
Diphtheria	Automated EIA (VaccZyme™ kit from The Binding Site Group) ^Δ	Diphtheria toxoid	1.0 IU/ml (WHO) 0.1 IU/ml (frequently cited)	DTaP/IPV 0.1-0.99: 1 booster dose <0.1 : 3 doses, 4 weeks apart	IDSA[3], EBMT[1]
Measles	Automated CLIA (DiaSorin Liaison®)	Recombinant measles virus antigen	15 AU/ml ^Ψ (assay)	MMR 2 doses, 12 weeks apart	IDSA[3], EBMT[1]
Mumps	Automated CLIA (DiaSorin Liaison®)	Recombinant mumps nucleoprotein	10 AU/ml ^Ψ (assay)	N/A	IDSA[3], EBMT[1]
Rubella	Automated CLIA (DiaSorin Liaison®)	Rubella-like particles	10 IU/ml ^Ψ (WHO)	N/A	IDSA[3], EBMT[1]
VZV	Automated CLIA (DiaSorin Liaison®)	Varicella zoster antigen	150 mIU/ml (assay)	Varivax 2 doses, 8 weeks apart	IDSA[3]
Confirmatory VZV^Φ	Manual EIA (VaccZyme™ kit from The Binding Site Group)	Purified VZV glycoprotein	150 mIU/ml (assay)	Varivax 2 doses, 8 weeks apart	IDSA[3]
Pneumococcal	12 Danish pneumococcal serotypes ^δ		1.0µg/ml (expert opinion) 0.35 µg/ml (WHO infants)	PCV-13; then PPV-23 2 months apart	UK Green Book[12]
Tetanus	In house EIA against NEQAS/local pooled controls ^θ	Tetanus toxoid	0.1 IU/ml (WHO)	DTaP/IPV 3 doses, 4 weeks apart	IDSA[3], EBMT[1]
Haemophilus influenzae type B	In house EIA against NEQAS/local pooled controls ^θ	Hib capsular polysaccharide fragments	0.15µg/ml (WHO)	Mentorix ^γ 3 doses, 4 weeks apart	IDSA[3], EBMT[1]

Abbreviations: EIA = Enzyme Immunoassay, CLIA = chemiluminescent immunoassays, IDSA = Infectious Diseases Society of America, EBMT = The European Society for Blood and Marrow Transplantation

^Δ processed at Birmingham Heartlands

^δ processed at Manchester Medical Microbiology Partnership, includes 12 of the 13 serotypes tested for are included in the PCV-13 vaccine (1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23) [12]

^ΦA second varicella assay was performed (VaccZyme) done on any equivocal results from the Liaison® VZV assay (100-150mIU/ml), as the VaccZyme™ EIA has been found to have a greater low level sensitivity [10].

^θ Reactions were measured spectrophotometrically and compared against standards from the NIBSC (National Institute for Biological Standards and Control) for tetanus, and the FDA (Food and Drug Administration) for Hib

^Ψ Reported qualitatively

^γ Pedicel recommended in lieu of Mentorix if Diphtheria/Tetanus immunisation was also required

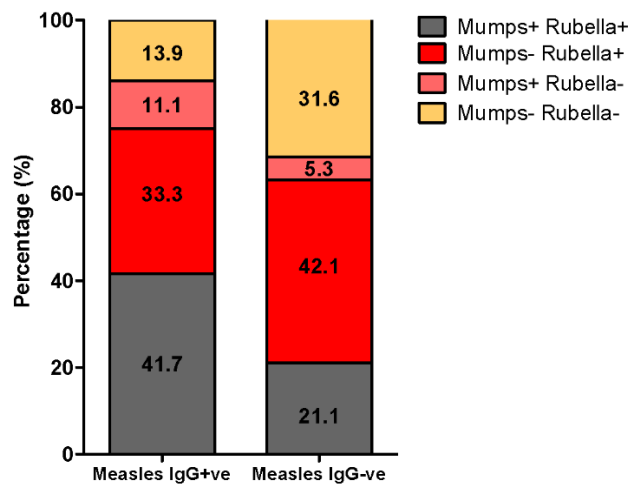
Supplementary Table 2a: By Danish serotype, pre-vaccination n=56 percentage of cohort under each threshold, and mean and median pneumococcal titres

Serotype	Percentage of cohort pre-vaccination		Antibody titre $\mu\text{g/ml}$	
	< 0.35 $\mu\text{g/ml}$	< 1.0 $\mu\text{g/ml}$	Median	Mean
1	71.4	83.9	0.08	0.79
3	83.9	96.4	0.05	0.21
4	83.9	91.1	0.05	0.33
5	80.4	87.5	0.05	1.17
6B	80.4	92.9	0.05	1.40
7F	57.1	80.4	0.27	1.91
9V	78.6	92.9	0.13	0.54
14	48.2	53.6	0.58	7.55
18C	64.3	80.4	0.19	1.61
19A	41.1	69.6	0.47	1.39
19F	57.1	76.8	0.24	1.29
23F	73.2	87.5	0.13	1.20

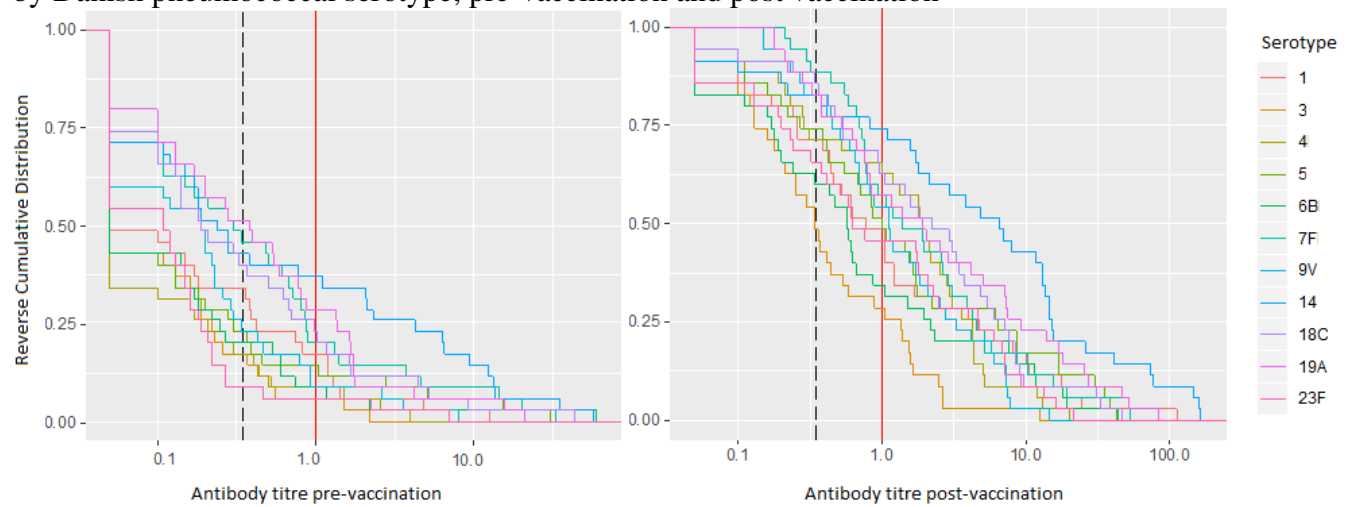
Supplementary Table 2b: By Danish serotype, post-vaccination n=35 percentage of cohort under each threshold, and mean and median pneumococcal titres

Serotype	Percentage of cohort post vaccination		Antibody titre $\mu\text{g/ml}$	
	< 0.35 $\mu\text{g/ml}$	< 1.0 $\mu\text{g/ml}$	Median	Mean
1	28.6	51.4	0.77	6.60
3	51.4	71.4	0.34	1.01
4	28.6	34.3	1.92	3.03
5	22.9	48.6	1.00	6.57
6B	40.0	65.7	0.57	3.91
7F	11.4	42.9	1.38	6.05
9V	17.1	45.7	1.11	2.52
14	0.0	25.7	6.55	24.10
18C	14.3	37.1	2.22	5.93
19A	17.1	42.9	1.93	9.83
19F	11.4	34.3	1.62	6.87
23F	34.3	54.3	0.63	3.27

Supplementary Fig 1. Mumps and Rubella serostatus based on Measles serostatus



Supplementary Fig 2: Reverse Cumulative Distribution Graph to show antibody titre levels by Danish pneumococcal serotype, pre-vaccination and post vaccination



Supplementary Table 3a: Univariate analysis (pre vaccination)

	Measles			Varicella			Mumps			Rubella			Pneumococcal		
	OR	p value	95% CI of OR	OR	p value	95% CI of OR	OR	p value	95% CI of OR	OR	p value	95% CI of OR	OR	p value	95% CI of OR
Gender															
- Female	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
- Male	2.42	0.138	0.77-8.23	4.80	0.166	0.70-95.57	1.87	0.256	0.64-5.63	3.5	0.058	1.01-14.30	0.56	0.357	0.15-1.89
Age (years)	1.09	0.005*	1.03-1.15	1.03	0.401	0.96-1.11	1.02	0.288	0.98-1.07	0.965	0.158	0.92-1.01	1.03	0.311	0.98-1.08
Age at auto (years)	1.07	0.008*	1.02-1.13	1.04	0.264	0.98-1.12	1.03	0.1322	0.99-1.07	0.982	0.356	0.94-1.02	1.02	0.418	0.98-1.06
Time since auto (years)	0.98	0.6252	0.92-1.05	0.96	0.488	0.86-1.07	0.96	0.216	0.89-1.02	0.986	0.703	0.92-1.06	1.01	0.873	0.93-1.08
Primary diagnosis															
- Autoimmune	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
- Lymphoma	1.69	0.619	0.18-15.54	2e-07	0.994	NA-3e+67	0.52	0.54	0.06-4.79	6e-08	0.993	NA-7e+90	1.15	0.906	0.13- 24.86
- Other malignancies	3.00	0.341	0.28-33.03	2e-07	0.994	NA - 8e+78	1.67	0.65	0.16-17.18	4e-08	0.993	NA-1e+90	0.69	0.781	0.06-16.71
Conditioning regimens															
- Other chemotherapy only conditioning	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
- ATG containing	0.18	0.177	0.01-2.21	3545401.03	0.994	1e-171-NA	0.44	0.487	0.04-4.80	2e+07	0.993	3e-77-NA	1.83	0.662	0.07-27.22
- BEAM containing	0.29	0.148	0.04- 1.32	0.63	0.688	3e-02-4.79	0.21	0.028*	0.05-0.80	1e+00	0.927	2e-01-4.16	1.90	0.454	0.40-13.84
- TBI containing	0.18	0.177	0.01- 2.21	0.25	0.373	8-7.56	0.44	0.487	0.04-4.80	4e-01	0.487	4e-02-4.80	5.50	0.177	0.45-79.84
Radiotherapy received pre-transplant															
- No	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
- Yes	1.37	0.587	0.44-4.45	0.69	0.668	0.12-4.06	0.99	0.984	0.33-2.92	1.29	0.678	0.40-4.45	1.00	1.00	0.80-13.73
Rituximab received pre-transplant															
- No	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
- Yes	6.92	0.077	1.17-132.75	1.28	0.829	0.18-26.02	0.69	0.588	0.16-2.61	1.12	0.882	0.27-5.71	3.33	0.090	0.80-13.73

Supplementary Table 3b: Multivariate analysis (pre vaccination)

	Measles			Mumps		
	OR	p value	95% CI of OR	OR	p value	95% CI
Gender						
- Female	-	-	-	-	-	-
- Male	1.94	0.383	0.44-9.32	2.33	0.207	0.64-9.22
Age (years)	1.10	0.011*	1.03-1.20	1.03	0.268	0.98-1.09
Conditioning regimens						
- Other chemotherapy only conditioning	-	-	-	-	-	-
- ATG containing	0.27	0.349	0.01-4.26	0.49	0.561	0.04-5.98
- BEAM containing	0.12	0.027*	0.01-0.66	0.15	0.013*	0.03-0.62
- TBI containing	0.04	0.029*	0.00-0.65	0.41	0.485	0.03-5.19
Rituximab received pre-transplant						
- No	-	-	-	-	-	-
- Yes	6.06	0.155	0.70-150.96	-	-	-

Supplementary Table 4: Univariate analysis (post vaccination)

	Pneumococcal			Diphtheria		
	OR	p value	95% CI	OR	p value	95% CI
Gender						
- Female	-	-	-	-	-	-
- Male	1.11	0.877	0.29-4.27	9.80	0.017*	1.72-83.05
Age (years)	1.01	0.866	0.94-1.07	1.05	0.311	0.96-1.15
Age at auto (years)	1.00	0.968	0.95-1.05	1.04	0.203	0.98-1.12
Time since auto (years)	1.01	0.725	0.93-1.11	0.95	0.335	0.85-1.05
Primary diagnosis						
- Autoimmune	-	-	-	-	-	-
- Lymphoma	2.60	0.461	0.22-60.78	3.62	0.994	4.96e-182 -NA
- Other malignancies	2.50	0.512	0.17-66.55	1.70	0.995	2.01e-145 - NA
Conditioning regimens						
- Other chemotherapy only conditioning	-	-	-	-	-	-
- ATG containing	0.50	0.638	0.02-8.51	8.65	0.997	NA-3.85e+241
- BEAM containing	1.30	0.775	0.20-8.41	8.50	0.087	0.72-1.21e+02
- TBI containing	2.00	0.638	0.12-58.79	8.65	0.996	NA – 9.86e+162
Radiotherapy received pre-transplant						
- No	-	-	-	-	-	-
- Yes	1.50	0.557	0.39-6.03	0.73	0.701	0.14-3.81
Rituximab received pre-transplant						
- No	-	-	-	-	-	-
- Yes	0.80	0.782	0.16-4.03	9.46	0.994	5.87e-76-NA

Supplementary Table 5: Multivariate analysis (post vaccination)

	Diphtheria		
	OR	p value	95% CI
Gender			
- Female	-	-	-
- Male	8.29e+00	0.158	5.4e-01-3.09e+02
Age (years)	1.15e+00	0.151	9.72-1.48e+00
Conditioning regimens			
- Other chemotherapy only conditioning	-	-	-
- ATG containing	5.84e-09	0.998	NA-∞
- BEAM containing	1.91e+01	0.123	6.79e-01-2.4e+03
- TBI containing	3.06e-09	0.997	NA-3.96e+287

Acknowledgements

We would like to thank our primary care and infectious diseases colleagues for their support in vaccinating our subset of patients. In addition, we are grateful to the biomedical scientists in Sheffield Laboratory Medicine for their help in processing and testing samples, particularly Geraldine Ball and Amina Bhayat-Cammack who helped compile Supplementary Table 1.

Diana Greenfield is a National Institute for Health Research (NIHR) Senior Nurse Research Leader. The views expressed in this article are those of the author and not necessarily those of the NIHR, or the Department of Health and Social Care.

References

- [1] Ljungman P, Cordonnier C, Einsele H, Englund J, Machado CM, Storek J, et al. Vaccination of hematopoietic cell transplant recipients. *Bone Marrow Transplant* 2009;44:521–6. <https://doi.org/10.1038/bmt.2009.263>.
- [2] Styczynski J, Tridello G, Koster L, Iacobelli S, van Biezen A, van der Werf S, et al. Death after hematopoietic stem cell transplantation: changes over calendar year time, infections and associated factors. *Bone Marrow Transplant* 2020. <https://doi.org/10.1038/s41409-019-0624-z>.
- [3] Rubin LG, Levin MJ, Ljungman P, Davies EG, Avery R, Tomblyn M, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. *Clin Infect Dis* 2014;58:309–18. <https://doi.org/10.1093/cid/cit816>.
- [4] Miller PDE, De Silva TI, Skinner R, Gilleece M, Peniket A, Hamblin A, et al. Routine vaccination practice after adult and paediatric allogeneic haematopoietic stem cell transplant: A survey of UK NHS programmes. *Bone Marrow Transplant* 2017. <https://doi.org/10.1038/bmt.2016.362>.
- [5] Gilleece MH, Towilson K, Wilson M, Littlewood T, Cook G, Marks DI. 203: Vaccination against infection after haemopoietic stem cell transplant. *Biol Blood Marrow Transplant* 2007;13:75. <https://doi.org/10.1016/j.bbmt.2006.12.207>.
- [6] Plotkin SA. Correlates of protection induced by vaccination. *Clin Vaccine Immunol* 2010;17:1055–65. <https://doi.org/10.1128/CVI.00131-10>.
- [7] World Health Organization. Weekly epidemiological record: Diphtheria Position Paper. *Wkly Epidemiol Rec* 2017;417–36. <https://doi.org/10.1016/j.actatropica.2012.04.013>.
- [8] Kennedy LB, Li Z, Savani BN, Ljungman P. Measuring Immune Response to Commonly Used Vaccinations in Adult Recipients of Allogeneic Hematopoietic Cell Transplantation. *Biol Blood Marrow Transplant* 2017;23:1614–21. <https://doi.org/10.1016/j.bbmt.2017.06.006>.
- [9] Daly TM, Hill R. Use and Clinical Interpretation of Pneumococcal Antibody Measurements in the Evaluation of Humoral Immune Function. *Clin Vaccine Immunol* 2015. <https://doi.org/10.1128/CVI.00735-14>.
- [10] Bailey H. Screening for varicella in pregnancy: External review against programme appraisal criteria for the UK National Screening Committee (UK NSC) 2015:1–27.
- [11] Maple PAC, Rathod P, Smit E, Gray J, Brown D, Boxall EH. Comparison of the performance of the LIAISON VZV-IgG and VIDAS automated enzyme linked fluorescent immunoassays with reference to a VZV-IgG time-resolved fluorescence immunoassay and implications of choice of cut-off for LIAISON assay. *J Clin Virol* 2009. <https://doi.org/10.1016/j.jcv.2008.08.012>.
- [12] Ramsay M. Pneumococcal: the green book, chapter 25. *Public Heal Engl* 2018:Last updated 18 Jan 2018.
- [13] Wagner KS, White JM, Andrews NJ, Borrow R, Stanford E, Newton E, et al. Immunity to tetanus and diphtheria in the UK in 2009. *Vaccine* 2012. <https://doi.org/10.1016/j.vaccine.2012.09.029>.
- [14] Ljungman P, Aschan J, Barkholt L, Broliden PA, Gustafsson B, Lewensohn-Fuchs I, et al. Measles immunity after allogeneic stem cell transplantation; influence of donor type, graft type, intensity of conditioning, and graft-versus host disease. *Bone Marrow Transplant* 2004. <https://doi.org/10.1038/sj.bmt.1704634>.
- [15] Ramsay M. Chapter 34 Varicella. *Green B* 2015;3:421–42.
- [16] Ramsay ME, McVernon J, Andrews NJ, Heath PT, Slack MP. Estimating Haemophilus influenzae Type b Vaccine Effectiveness in England and Wales by Use of the Screening Method . *J Infect Dis* 2003. <https://doi.org/10.1086/376997>.
- [17] Bollaerts K, Riera-Montes M, Heininguer U, Hens N, Souverain A, Verstraeten T, et al. A systematic review of varicella seroprevalence in European countries before universal childhood immunization: Deriving incidence from seroprevalence data. *Epidemiol Infect* 2017. <https://doi.org/10.1017/S0950268817001546>.
- [18] England PH. Guidelines on Post-Exposure Prophylaxis for measles 2019:1–24.
- [19] Guzek A, Berghoff AS, Jasinska J, Garner-Spitzer E, Wagner A, Stiasny K, et al. Reduced seroprevalence against vaccine preventable diseases (VPDs) in adult patients with cancer: necessity of routine vaccination as part of the therapeutic concept. *Ann Oncol* 2020. <https://doi.org/10.1016/j.annonc.2019.11.005>.
- [20] Sheridan SL, Frith K, Snelling TL, Grimwood K, McIntyre PB, Lambert SB. Waning vaccine immunity in teenagers primed with whole cell and acellular pertussis vaccine: Recent epidemiology. *Expert Rev Vaccines* 2014. <https://doi.org/10.1586/14760584.2014.944167>.